

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Appellants : Ivan KING and Li-Mou ZHENG
U.S. Serial No. : 10/738,423
Confirmation No. : 8783
Filed : December 16, 2003
Art Unit : 1633
Examiner : Qian Janice Li
For : COMPOSITIONS AND METHODS FOR TUMOR-
TARGETED DELIVERY OF EFFECTOR MOLECULES

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June 29, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

**APPELLANTS' REPLY BRIEF TO EXAMINER'S SUPPLEMENTAL ANSWER
PURSUANT TO 37 CFR § 41.41**

A Supplemental Examiner's Answer was mailed on May 11, 2009. Appellants may file a Reply Brief to the Supplemental Examiner's Answer within two months from the date of the Supplemental Examiner's Answer. Accordingly, this Reply Brief is timely filed. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

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REPLY BRIEF

This Reply Brief is filed in response to the Supplemental Examiner's Answer mailed May 11, 2009. Claims 113, 115-117, and 119-124 are currently under appeal. Independent claim 113 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB⁻ mutant. The present specification discloses a mutant msbB⁻ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with cytoxan or cisplatin (page 104, line 1 to page 106, line 20). Dependent claims 115-117 define the solid tumor or cancer, and the subject (a mammal or a human). Dependent claim 119 specifically delimits the claim to administration of an effective amount of cisplatin. Dependent claims 121-122, which are duplicates, specifically delimit the method of claim 115 to a lung cancer.

Independent claim 123 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of an anti-cancer compound and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB⁻ mutant. The present specification discloses a mutant msbB⁻ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with an anti-cancer compound (page 104, line 1 to page 106, line 20). Dependent claim 124 specifically delimits the claim to administration of an effective amount of cisplatin.

I. 35 U.S.C. 103(a) Rejection: Response to Examiner's Arguments in Supplemental Examiner's Answer

A. References Cited in Appellants' Reply Brief: Unpredictability in the Art

The Supplemental Examiner's Answer states that claims 113, 116, 117, 119, 120, 123, 124 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (Nat. Biotech. 17:37-41 (1999)) in view of Schachter et al. (Cancer Biother. Radiopharm. 13:155-64 (1998)).

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In the Appellants' Reply Brief of March 12, 2009, Appellants argued against the line of reasoning contained in the Examiner's Answer of February 5, 2009. The Examiner argued that "the bacteria therapy has been proven effective in treating melanoma as taught by *Low et al.*, and the cisplatin has been proven effective in treating melanoma as shown by *Schachter et al.*": therefore "it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of melanoma with a reasonable expectation of success." Page 10 of Examiner's Answer of February 5, 2009. In support of this proposition, the Examiner cited *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) for the proposition that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art." *Id.*

Appellants disputed the application of *In re Kerkhoven*, a case involving combinations of spray-dried detergents, as overly simplistic with respect to the obviousness analysis of the presently claimed invention, drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*. In distinguishing the low level of unpredictability in the art present in *In re Kerkhoven* from the high level of unpredictability in the chemotherapeutic arts, Appellants recited three examples of chemotherapeutic combinations, which were admittedly chemical in nature, showing synergistic effects, antagonistic effects, or exhibiting no measurable effect. These were *Chow et al.* (abstract, Leuk. Lymphoma 2003), *Budman et al.* (abstract, Anticancer Drugs 2002), and *Dasmahapatra et al.* (Clin. Cancer Res. 2004). The Examiner has countered that the arguments were not found persuasive for four separate reasons; the Appellants wish to address the applicable reasons in turn.

The Examiner's second and third arguments will be addressed. The Examiner states that "*Dasmahapatra* provides reasoning for combine[sic] and reports synergistic effect between two chemotherapeutic agents. All three references have shown synergistic effects when combining

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certain chemotherapeutic compounds.” Page 3, Examiner’s Supplemental Answer, May 11, 2009. Here, the Examiner has conveniently omitted the primary reason why each of the references was cited. While all three references may show synergistic effects with respect to certain chemotherapeutic drug combinations, two of the references evidenced additive if not antagonistic effects, and all three cited references demonstrated that experimentation was necessary in order to determine whether synergism would present or to determine the extent of hypothesized synergism. For instance, *Chow et al.* states: “[E]ffects of the combination of Ara-C with bendamustine, a new bifunctional agent with alkylating activity and a purine nucleus, was investigated. Assessment by combination index analysis showed that Ara-C combined with fludarabine or bendamustine exhibited **additive to antagonistic effects** on inhibition of cell proliferation, induction of apoptosis as well as on disruption of mitochondrial membrane potential, independent of a simultaneous or consecutive (purine analogues before Ara-C) incubation schedule. In contrast, the combination of Ara-C with 2-CdA exclusively yielded synergistic effects.” *Budman et al.* states: “Docetaxel combined with either epirubicin or doxorubicin displayed cytotoxic synergistic effects in hormone-refractory DU 145 and PC 3 cell lines. **In contrast, drugs which have been combined clinically to treat hormone-refractory prostate cancer, i.e. cisplatin, carboplatin or etoposide, were antagonistic when combined with docetaxel.**” *Dasmahapatra et al.* investigated whether combining chemotherapeutic agents “targeting distinct components of the same growth regulatory pathway” would, in effect, create a synergism which “might lead to more complete modulation of the target pathway at concentrations lower than those associated with limiting adventitious toxicities from either agent alone,” i.e. would prevent unacceptable toxicity.

In argument 3, the Examiner concludes that, “The references illustrated that the skilled in the art were fully aware that the combination of chemical compounds may work synergistically, antagonistically, or may act without any measurable effect. [...] Any experimentation for affirmation of a combination effect would be considered routine experimentation....” Appellants would like to point out that these possible outcomes are the fundamental outcomes faced by any party performing an experiment or engineering endeavor: a combination of elements may function better than previous elements, may work no better than previous elements, or may function more

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poorly than previous elements. The fact that these are the three possible outcomes faced by an inventor is in no way indicative of whether there exists a high level of predictability in the art, nor is it indicative of whether a particular outcome would be *prima facie* obvious, nor is it indicative that an inventor would have a reasonable expectation of success in any particular combination.

In stating that experiments were done for "affirmation," the Examiner wrongly characterizes the nature of the experimentation. There is no evidence that *Chow et al.*, *Budman et al.*, or *Dasmahapatra et al.* were assured of the results of their experiments, or that the outcomes of their experiments were predestined. Also, the Examiner has cited the presence of a "combination index" in *Budman et al.* for the proposition that experiments involving drug combinations would be merely "routine experimentation". Page 4, Examiner's Supplemental Answer, May 11, 2009. Appellants counter that the presence of a system of measurement for an outcome (which is what the "combination index" would appear to be), is likewise not indicative of whether there exists a high level of predictability in the art, nor is it indicative of whether a particular outcome would be *prima facie* obvious, nor is it indicative that an inventor would have a reasonable expectation of success in any particular combination. Without justification, the Examiner is systematically attempting to deny the level of unpredictability in the art.

In addition, in her fourth argument, the Examiner has objected to Appellants' use of the term "antagonism," stating that "'antagonism' refers to interference in the physiological action of a chemical substance by another having a *similar structure*," further stating that "this is not the case for instant rejections[sic], wherein the references relied on are not a combination between two chemotherapeutic agents, but between a routine chemotherapeutic regimen and a bacteria therapy via a very different approach for killing cancer cells. No structural similar[sic] compounds are involved between the two approaches nor do they target the same signaling pathway. Hence, it is unlikely an antagonistic effect would occur when one combines the two." Page 4, Examiner's Supplemental Answer, May 11, 2009.

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Appellants' utilized the *Chow et al.*, *Budman et al.*, and *Dasmahapatra et al* references to show unpredictability in the art. Admittedly, none of these references utilize a bacterial anti-tumor treatment. And Appellants' are well-aware that their claimed invention involves a method implicating a chemotherapeutic agent and a tumor-targeted bacterium. However, it is precisely because of the nonobviousness and novelty of the present invention that Appellants relied on references in the chemotherapeutic arts relating to combinations of anti-tumor drugs as a close analogous art: Appellants do not sufficiently possess references necessary to define predictability with respect to the combination of a chemotherapeutic and a bacterial therapy. Thus, when Appellants employ the terms "antagonism" or "antagonistic," they are not doing so in the context of a purely pharmacologic interaction between chemotherapeutic agents "having similar structure or targeting the same signaling pathway". They are instead employing the term as it is known in common usage, i.e. the second definition used in the Merriam-Webster online dictionary: "opposition in physiological action; *especially*: interaction of two or more substances such that the action of any one of them on living cells or tissues is lessened".¹ Furthermore, Appellants wish to point out that it would be logically impermissible for the Board to permit the Examiner to broadly define the art when rejecting the Appellants' claims (allowing the Examiner to argue obviousness pursuant to *In re Kerkhoven*, so that a combination of "two known compositions... useful for the same purpose" is prima facie obvious, Page 9 of Examiner's Answer of February 5, 2009), while concurrently permitting the Examiner to narrowly define the art when Appellants are attempting to show non-obviousness and unpredictability (rejecting Appellants' evidence because the "chemotherapeutic regimen and... bacteria therapy" act "via a very different approach", Page 4 of Examiner's Supplemental Answer of May 11, 2009).

As to the Examiner's First Argument, the Examiner stated that, "The references provide confirmation in terms of motivation for combining different therapeutic regimens in cancer treatment," and that, "Apparently, there are needs and more than one strategy[sic] to design a therapeutic combination regimen." Page 3 of Examiner's Supplemental Answer of May 11, 2009.

¹ Merriam Webster's Online Dictionary, Entry for "Antagonistic," <http://www.merriam-webster.com/dictionary/antagonism> (last visited June 3, 2009).

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Although the Examiner has not offered credible evidence that Appellants' own combinations would result in predictable results, or that Appellants' have chosen from a number of identified, predictable solutions with a reasonable expectation of success, or that there was a sufficient teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill in the art to combine prior art reference teachings to arrive at the claimed invention, the notion that need for better anticancer therapies or methods suffices as evidence of obviousness in the combination has been echoed numerous times throughout prosecution. To the contrary, Appellants counter that the well-recognized need for anticancer therapeutics or methods is a secondary consideration (i.e. a "long-felt and unmet need") in support of non-obviousness. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996), for the proposition that secondary considerations of non-obviousness include the commercial success of the invention at issue and its satisfaction of a long-felt need; *see also, The Procter and Gamble Co. v. Teva Pharms. USA, Inc.*, 279 U.S. App. LEXIS 10475, *18-19 (Fed. Cir. May 13, 2009), ruling that a district court did not commit clear error by supporting a finding of non-obviousness after a showing of secondary considerations that the drug in question treated a disease (osteoporosis) "recognized as a serious disease" where "existing treatments were inadequate."

B. Synergistic Results

Appellants have taken note of the Examiner's remarks starting on page 5 of the Supplemental Examiner's Answer of May 11, 2009 respecting synergism. The Examiner addressed the effects of cytoxan and VNP20009. The Examiner argued against synergism, stating that "the effect may be better described as additive and expected at day 25 and slightly more than additive at day 30." She further explained that "considering biological responses do not often follow strict mathematics, variations are seen more often than not between and within experiments, the degree of differences in the table among different groups at day 30 would still be considered as within a reasonable expectation, not entirely unexpected." *See* Page 6, Supplemental Examiner's Answer of May 11, 2009.

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Appellants believe that the experimental results speak for themselves. Appellants note that of effects which are "more than additive at day 30" could more easily be characterize as "synergistic," and therefore unexpected.

With respect to the Examiner's remarks regarding the necessity of limitations to cytoxan and VPN20009 of *Salmonella*, Appellants, as required, are arguing the claims to the application as entered. However, Appellants underscore that on March 29, 2007, they presented an amendment in response to the Final Office Action of December 14, 2006. These claims were specifically limited to methods implicating only cytoxan and cisplatin as the recited chemotherapeutic drugs. Claims presented on May 24, 2007 with a Request for Continued Examination were limited to methods implicating only cytoxan and cisplatin as chemotherapeutic drugs. Without conceding the correctness of any points made in the corresponding section of Examiner's Supplemental Answer, which do not appear to speak to issues of obviousness, but instead appear to address 35 U.S.C. 112 rejections that have already been surmounted, Appellants have been quite willing to limit claims to these recited chemotherapeutic drugs and would be willing to make such limitations for issuance of a patent. Appellants herewith submit amendments to the claims pursuant to 37 CFR 41.33.

C. Mechanism of Action of Attenuated Tumor-Targeted *Salmonella* and Examiner's Use of *Jirillo et al.* Reference

The obviousness rejection of the claims under 35 U.S.C 103 is made over *Low et al.* in view of *Schachter et al.* In the Examiner's Answer, the Examiner had stated:

"[C]onsidering that the biotherapy taught by *Schachter et al.* is for priming and immune regulation, there was evidence in the prior art showing that attenuated *Salmonella* also have priming and immune regulation effect. *Jirillo et al.* (Int J Immunopharmacol 1986;8:881-6) teaches that attenuated *Salmonella* bacteria enhanced immune responsiveness in patients with gynecologic malignancies via immune regulation (see e.g. the abstract). Thus, attenuated *Salmonella* taught by *Low* has similar underlying principle as does the biotherapy taught by *Schachter* in treating cancer. Accordingly it was not counterintuitive for the skilled to combine the bacteria therapy with the conventional therapy when used with caution." Page 13, Examiner's Answer of February 5, 2009.

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The Examiner's notion was clearly to show that *Schachter et al.*, which presented a stimulatory cytokine therapy in conjunction with a chemotherapy, "supplemented *Low et al.* by illustrating it was known in the art to combine a routine chemotherapeutic regimen with a newly developed biotherapy in treating solid tumors such as melanoma." Page 6, Examiner's Answer of February 5, 2009. *Low et al.* allegedly supplies the "biotherapy" to be combined with a chemotherapeutic regimen, while *Schachter et al.* demonstrates that it is routine to combine a "biotherapy" with a routine chemotherapeutic regimen.

Appellants believed it clear that the Examiner regarded a "biotherapy," such as the one found in *Low et al.*, an attenuated *Salmonella*, as interchangeable in principle with the "biotherapy" of *Schachter et al.*, an immune-priming cytokine therapy. The Examiner argued that the attenuated *Salmonella* biotherapy of *Low et al.* was sufficiently akin to the biotherapy of *Jirillo et al.*, i.e. a biotherapy that produced "enhanced immune responsiveness," to demonstrate that the biotherapy of *Low et al.* operated on the same "underlying principle" as the biotherapy of *Schachter et al.*, i.e., that it also was a therapy with priming and immune regulation effect, thus rendering the biotherapy of *Low et al.* nothing more than an obvious substitute in *Schachter et al.*'s illustration.

The Appellants' Reply Brief of March 12, 2009 set forth that the Examiner had erred by equating the underlying mechanism of action in *Low et al.* to that of *Jirillo et al.*, and thus simultaneously erred in assessing that the type of biotherapy presented in *Low et al.* was akin to, or interchangeable with the type of biotherapy as *Schachter et al.* If the underlying mechanism of the biotherapy presented in *Low et al.* was not akin to that of *Jirillo et al.* nor equivalent to that of *Schachter et al.*, and if the combination of the biotherapy of *Low et al.* was actually counterintuitive (as Appellants argued), then *Schachter et al.* could no longer provide the basis for demonstrating what would otherwise be an obvious substitution.

The Examiner now states in the Supplemental Examiner's Answer of May 11, 2009 that "It is in the context of immune regulation that the Office concluded that the attenuated *Salmonella* taught by *Low* has similar underlying principle as does the biotherapy taught by *Schachter* in treating cancer

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because... it is undeniable that both *Low* and *Jirillo* had safely used the attenuated *Salmonella* for treating tumor." The examiner further notes that, "*Jirillo* proves that the attenuated *Salmonella* could enhance immune responsiveness in cancer patients, it would likely be the case for *Low* even though he did not explicitly teach such." Page 7, Supplemental Examiner's Answer of May 11, 2009.

Appellants wish to explain again the fundamental problem with the Examiner's approach. It is not clear that the bacteria of *Jirillo et al.* can actually be considered attenuated, and to the extent that the bacteria has been modified, it was modified in a diametrically opposite fashion to the bacteria of *Low et al.* *Jirillo et al.* maintains that which *Low et al.* specifically sought to eliminate: the lipid A moiety of a bacterial lipopolysaccharide (LPS). The bacteria of *Jirillo et al.* were treated with acetic acid and placed in a boiling water bath "to cleave the acid labile bond between the chetodeoxyoctonate and the lipid A on the bacteria surface" while retaining the Lipid A itself. *Jirillo et al.* pp. 881-882. *Jirillo et al.* specifically tested whether lipid A performed an immune priming or immune boosting function in cancer patients, and found that the lipid A performed such functions. *Jirillo et al.*, Abstract. In contrast, *Low et al.* went to great lengths to modify their bacteria so as to lessen the harmful effects of Lipid A (such as "TNA α septic shock stimulated by lipid A"), and to increase safety by creating a bacteria with a mutant Lipid A (See *Low et al.*: "In *E. coli*, the *MsbB* (*mlt*) gene is involved in the terminal myristoylation of lipid A. Genetic disruption of this gene in *E. coli* results in a stable nonconditional mutation that lowers TNF α induction up to 10-fold by whole bacteria or up to 10,000 fold by purified lipopolysaccharide (LPS)," and "As little as 1 ng of LPS from wild type was sufficient to elicit a measurable TNF α response, which was maximal at 10 ng. In contrast, 100 μ g of *msbB* LPS were insufficient to generate any response"). *Low et al.*, Abstract, p. 1 and p. 38. Although the Examiner stated that, "[I]t would likely be the case for *Low* [that the *Salmonella* of *Low* would enhance immune responsiveness in the manner of *Jirillo*] even though he did not explicitly teach such," *Low et al.*'s bacteria did not attempt to achieve, nor did it possess any function intended to enhance immune responsiveness, and it especially did not attempt to enhance immune responsiveness through the identified mechanism of *Jirillo et al.*, lipid A.

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In that the disclosed tumor-targeted bacteria of the present invention did not act as an immune priming or immune boosting therapy, it again differs from the immune priming or immune boosting bacteria of *Jirillo et al.*

Additionally, as pointed on in Appellants' Reply Brief of March 12, 2009, Appellants' May 24, 2007 Supplemental Amendment in Response to the December 14, 2006 Final Office Action remarked that Appellants' use of tumor-targeted bacteria in a combination chemotherapy regimen goes against commonly accepted thinking in the chemotherapeutic arts. Page 8 of Appellants' Supplemental Amendment of May 24, 2007. Appellants utilized Frifeld et al., (2004), *Fever in the Neutropenic Cancer Patient*, Chap. 46, Clinical Oncology, (3rd ed.) for the proposition that, "It is known that chemotherapy often results in a severe decrease of neutrophils, a condition known as neutropenia. A major result is a severely compromised ability of the cancer patient to fight infection against bacterial and fungal infections. [...] It is known that when unopposed by innate neutrophil responses bacterial infections spread quickly and relentlessly." *Id.* Therefore, Applicants again wish to emphasize this point, that in respect of combination therapies encompassing a chemotherapy and a biotherapy, the present combination is particularly counterintuitive and non-obvious in light of the consequences to a subject's immune system, such as neutropenia, upon administration of chemotherapies.

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In summary, Appellants submit that the Examiner has not made a legally or factually sufficiently claim of obviousness under 103(a), and that Appellants have sufficiently rebutted all claims to alleged obviousness over the prior art. Appellants thus respectfully request allowance of the present application.

Respectfully submitted,

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